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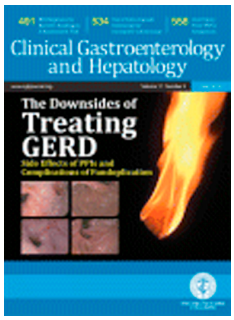

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Appropriate Therapeutic Drug Monitoring of Biologic Agents for Patients With Inflammatory Bowel Diseases

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Short title: Therapeutic drug monitoring of biologics in IBD

ABBREVIATIONS: ADA: anti-drug antibodies; ATI: antibodies to infliximab; CD: Crohn's disease, CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; IBD: inflammatory bowel disease; IMM: immunomodulator; TDM: therapeutic drug monitoring; TNF: tumor necrosis factor, UC: ulcerative colitis, PNR: primary non response, SLR: secondary loss of response, PK: pharmacokinetic, PD: pharmacodynamic, RCT: randomized controlled trial.

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Abstract

Background & Aims: Therapeutic drug monitoring (TDM) is widely available for biologic therapies in patients with inflammatory bowel disease (IBD). We reviewed current data and provided expert opinion regarding the clinical utility of TDM for biologic therapies in IBD.

Methods: We used a modified Delphi method to establish consensus. A comprehensive literature review was performed regarding the use of TDM of biologic therapy in IBD and presented to international IBD specialists. Subsequently, 28 statements on the application of TDM in clinical practice were rated on a scale of 1 to 10 (1=strongly disagree and 10=strongly agree) by each of the panellists. Statements were accepted if 80% or more of the participants agreed with a score ≥7. The remaining statements were discussed and revised based on the available evidence followed by a second round of voting.

Results: The panel agreed on 24 (86%) statements. For anti-tumor necrosis factor (anti-TNF) therapies, proactive TDM was found to be appropriate after induction and at least once during maintenance therapy, but this was not the case for the other biologics. Reactive TDM was appropriate for all agents both for primary non-response and secondary loss of response. The panellists also agreed on several statements regarding TDM and appropriate drug and anti-drug antibody (ADA) concentration thresholds for biologics in specific clinical scenarios.

Conclusion: Consensus was achieved towards the utility of TDM of biologics in IBD, particularly anti-TNF therapies. More data are needed especially on non-anti-TNF biologics to further define optimal drug concentration and ADA thresholds as these can vary depending on the therapeutic outcomes assessed.

KEY WORDS: consensus statement; Crohn's disease; ulcerative colitis; immunogenicity; anti-TNF; vedolizumab; ustekinumab.

INTRODUCTION

Biologic therapies, including the anti-tumor necrosis factor (anti-TNF) agents (infliximab, adalimumab, certolizumab pegol and golimumab), the adhesion molecule inhibitors (vedolizumab and natalizumab), and the p-40 interleukin-12/23 inhibitor ustekinumab, are effective treatments for patients with moderate to severe inflammatory bowel disease (IBD).[1, 2] Nevertheless, up to 1/3 of patients with Crohn's disease (CD) and ulcerative colitis (UC) show primary non-response (PNR) to biologic therapies and up to 50% of patients after an initial clinical response stop therapy either for secondary loss of response (SLR) or a serious adverse event.[3, 4] Both PNR and SLR are due to either pharmacokinetic (PK) or pharmacodynamic (PD) problems. PK issues are associated with inadequate drug exposure, often due to the development of anti-drug antibodies (ADA), whereas PD issues are typically related to inflammatory process unrelated to the targeted immunoinflammatory pathway.[5, 6]

Numerous studies have demonstrated a positive correlation between serum biologic drug concentrations and favorable therapeutic outcomes, while low or undetectable drug concentrations can lead to immunogenicity and treatment failure (**Tables 1-3 and supplementary table 1**).[7-95] Therapeutic drug monitoring (TDM), defined as the assessment of drug concentrations and ADA, is an important tool for optimizing biologic therapy. Reactive TDM has rationalized the management of PNR and SLR and has proven more cost-effective when compared to empiric dose escalation.[96-102] Preliminary data suggest that proactive TDM, with drug titration to a target trough concentration, performed in patients with clinical response/remission can also improve the efficacy of anti-TNFs.[38, 39, 103, 104] Moreover, proactive TDM may also improve the cost-effectiveness and safety of biologic therapy via the implementation of a de-escalation strategy in patients with supra-therapeutic drug concentrations by reducing the dose, increasing the time interval and/or stopping the immunomodulator in patients on combination therapy (optimized monotherapy).[39, 82, 105-107]

However, there are still some limitations when applying TDM into clinical practice, such as when to utilize TDM, proper interpretation and application of the results, and the identification of the optimal window/thresholds to target. These therapeutic windows or thresholds appear to vary based on the outcome of interest and the IBD phenotype (**Tables 1 and 2 and supplementary table 1**). Moreover, most of the data on implementation of TDM refer to anti-TNF therapies and the maintenance phase of treatment.

We aimed to reach a consensus on when and how to utilize TDM of biologic therapies during different phases of the treatment (i.e. induction, post-induction, and maintenance therapy) and sought to identify clinically relevant drug concentrations and ADA thresholds to help physicians apply TDM in clinical practice.

METHODS

We applied a modified Delphi method to establish consensus similar to that described in the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) program.[108] A comprehensive literature review was performed regarding the use of TDM of biologic therapies in IBD using PubMed and Medline databases. We utilized the search terms: 'inflammatory bowel disease'; 'Crohn's disease'; 'ulcerative colitis'; 'anti-drug antibodies'; 'therapeutic drug monitoring' AND 'infliximab' OR 'adalimumab' OR 'certolizumab pegol' OR 'golimumab' OR 'vedolizumab' OR 'ustekinumab'. The literature was then presented to a panel of 13 international IBD specialists. Subsequently, based on this review, 28 statements were formulated (K.P., A.S.C, C.A.S.) describing when and how to apply TDM in clinical practice. An Expert Consensus Development Meeting consisting of members of the BRIDGe group (www.BRIDGeIBD.com) and TDM specialists was held in New Orleans, on December 9, 2017, to refine and vote anonymously on the statements. Each statement was rated on a scale of 1 to 10 (1=strongly disagree, 10=strongly agree). Statements were accepted if 80% or

more of the participants agreed with a score ≥7. If less than 80% of the panelists agreed with a score ≥7, statements were discussed and revised based on the available evidence followed by a second round of voting. The word 'appropriate' was used for each statement to suggest that application of TDM for treatment optimization in a particular clinical scenario is a good option. However, these are not recommendations applicable to every patient.

RESULTS

The panel reached consensus on 24 out of 28 (86%) statements (**Tables 4 and 5**).

Scenarios when TDM of biologic therapies should be performed

Anti-TNF therapy

Based on the literature review, consensus was reached on all 4 statements regarding anti-TNFs (**Table 4A**).

1. It is appropriate to order drug/antibody concentration testing in responders at the end of induction for all anti-TNFs.

2. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on all anti-TNFs.

3. It is appropriate to order drug/antibody concentration testing of anti-TNFs at the end of induction in primary non-responders.

4. It is appropriate to order drug/antibody concentration testing for all anti-TNFs in patients with confirmed secondary loss of response.

Numerous studies have demonstrated a positive correlation between anti-TNF drug concentrations and favorable therapeutic outcomes (**Table 1, Table 2A and 2B, supplementary table 1**). However, the great majority of TDM studies refer to infliximab. A large retrospective study showed that at least one TDM, either proactive and/or reactive of

infliximab compared to lack of any TDM was associated with less treatment failure.[109] Several studies have shown that reactive TDM can better identify the cause and consequently manage SLR to anti-TNF therapy, although the data for PNR are more scarce.[4, 8, 10, 110, 111] Reactive TDM to guide infliximab dose adjustment compared to clinical decision making alone is associated with higher post-adjustment clinical response and endoscopic remission and fewer hospitalizations.[37] Moreover, reactive TDM of infliximab was found more cost-effective than utilizing clinical symptoms alone to guide therapeutic decisions.[99, 101, 102, 112]

Proactive TDM of infliximab compared to empiric dose escalation and/or reactive TDM was found to be associated with increased drug retention.[39] The landmark randomized controlled trial (RCT), Trough Concentration Adapted Infliximab Treatment (TAXIT), despite failing to meet its primary endpoint, showed that proactive TDM of infliximab compared to clinically-based dosing was associated with lower frequency of undetectable drug concentrations and lower risk of relapse.[104] Additionally, in patients with CD and subtherapeutic drug concentrations a one-time dose optimization improved clinical remission rates and C-reactive protein.[104] Furthermore, proactive compared to reactive TDM of infliximab was associated with greater drug durability, less need for IBD-related surgery or hospitalization, and lower risk of antibodies to infliximab or serious infusion reactions.[38] Recently, proactive following reactive TDM of infliximab was found to be associated with greater drug persistence and fewer IBD-related hospitalizations than reactive TDM alone.[103] Proactive TDM can also efficiently guide immunomodulator withdrawal in patients on combination therapy. This concept of 'optimized monotherapy' was introduced in a retrospective study showing that patients with infliximab concentrations ≥5 μg/mL had similar drug persistence when treated with infliximab monotherapy or combination therapy with an immunomdulator[5] and is further supported by a recent post-hoc analysis of the RCT Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) which

demonstrated that patients stratified by infliximab trough quartiles had comparable outcomes regardless of concomitant azathioprine.[113]

Vedolizumab

Consensus was reached on only 2 out of 4 statements regarding vedolizumab (**Table 4B**).

7. It is appropriate to order drug/antibody concentration testing for vedolizumab in non-responders at the end of induction.

8. It is appropriate to order drug/antibody concentration testing for vedolizumab in patients with confirmed secondary loss of response.

The current evidence supporting the role of TDM regarding vedolizumab derives only from exposure-response relationship studies showing that higher vedolizumab concentrations are associated with better therapeutic outcomes (**Table 2C**).[90-92, 114] In particular, a large single-center retrospective cohort study of 179 patients (66 with UC and 113 with CD) showed that higher vedolizumab trough concentrations at week 2 and 6 were associated with a higher probability of attaining endoscopic healing, clinical response and biologic response or remission assessed at week 14 for UC and week 22 for CD.[90] A multi-center prospective observational study identified a vedolizumab trough concentration cut-off of 18 μg/mL at week 6 as the only independent variable associated with mucosal healing within the first year of treatment.[91] Currently, there are no studies comparing either proactive or reactive TDM with symptom-based vedolizumab optimization.

Ustekinumab

Consensus was reached on only 2 out of 4 statements regarding ustekinumab (**Table 4C**).

11. It is appropriate to order drug/antibody concentration testing for ustekinumab in non-responders at the end of induction (at 8 weeks).

12. It is appropriate to order drug/antibody concentration testing for ustekinumab in patients with confirmed secondary loss of response.

The current evidence supporting the role of TDM regarding ustekinumab is based on two exposure-response relationship studies showing that higher ustekinumab concentrations correlate to better therapeutic outcomes (**Table 2D**).[49, 89] At this time, there are still no studies comparing either proactive or reactive TDM with empiric ustekinumab optimization.

Assays, drug concentrations and anti-drug antibodies

General

Consensus was reached on all 4 statements regarding the use of biologic drug concentrations and anti-drug antibodies (**Table 5A**).

13. There is no difference in indication for ordering drug/antibody concentrations or interpretation of results for biosimilars or originator drug.

Current data suggest that infliximab enzyme-linked immunosorbent assay (ELISA)s for evaluating either drug concentrations or ATI are suitable for monitoring the infliximab biosimilars SB2 and CT-P13.[115-118]

14. The threshold drug concentration may vary depending on disease phenotype and desired therapeutic outcome.

Numerous studies have shown an association between higher induction or maintenance biologic drug concentrations and favorable therapeutic outcomes in IBD (**Tables 1 and 2, supplementary table 1**). Current exposure-response relationship studies suggest that biologic drug concentration thresholds and ranges appear to differ depending on treatment goals and/or disease phenotypes. In general, higher drug concentrations tend to be associated with

more stringent outcomes and higher drug concentrations appear to be needed for phenotypes with a higher inflammatory burden, such as fistulising CD (**Tables 1 and 2, supplementary table 1, Figure 1**).

15. In the presence of adequate trough drug concentrations, anti-drug antibodies are unlikely to be clinically relevant.

A study from Steenholdt et. al. showed that most antibodies to infliximab (ATI) detected via the drug tolerant homogeneous mobility-shift assay (HMSA) lack neutralising potential when tested via a functional cell-based reporter-gene assay, suggesting that they may not be clinically significant.[119] A post-hoc analysis of the TAXIT study, which investigated the additional benefit of a drug-tolerant assay, concluded that although it allowed closer follow-up of ATI concentrations and identification of true transient versus persistent antibodies, it offered no clinical benefit over a drug-sensitive assay.[120] Nevertheless, other studies have suggested that 'double positive' patients (with positive ATI and drug on board) may be prone to SLR or lack of mucosal healing.[60, 67, 121]

16. Other than for anti-infliximab antibodies, there are not enough data to recommend a threshold for high anti-drug antibody titers for the biologic drugs.

Numerous studies have shown that ADA are associated with sub-therapeutic drug trough concentrations, loss of response and lack of recapture of response following dose escalation (**Table 3**).[10, 12-17, 21, 23, 27-29, 31-33, 37, 56-58, 60, 63, 67, 73, 75, 80-88] However, the great majority of them and specifically the ones suggesting a threshold of high-titer ADA refer to ATI (**Table 3**).

Infliximab

Consensus was reached on all statements regarding infliximab concentrations and ATI (**Table 5B**).

17. The current evidence suggests that the variability of infliximab concentrations between the different assays is unlikely to be clinically significant.

18. There is insufficient evidence that inter-assay drug concentration results are comparable for biologic drugs other than for infliximab.

Current evidence suggests that although absolute drug concentrations can differ between different assays, including the commonly used ELISA, radio-immunoassay, HMSA and the recently developed electrochemiluminescence immunoassay, they correlate well and generally lead to the same therapeutic decision.[83, 119, 122-124] However, these data refer mostly to infliximab, while there are only scarce data for adalimumab and none for non-anti-TNF agents.

19. The minimal trough concentration for infliximab post-induction at week 14 should be greater than 3 µg/ml, and concentrations greater than 7 µg/ml are associated with an increased likelihood of mucosal healing.

20. During maintenance the minimal trough concentration for infliximab for patients in remission should be greater than 3 µg/ml. For patients with active disease infliximab should generally not be abandoned unless drug concentrations are greater than 10 µg/ml.

These drug concentration thresholds were mainly based on infliximab exposure-response relationship studies depicted in **supplementary table 1**.

21. In the absence of detectable infliximab, high titer anti-infliximab antibodies require a change of therapy. Low level antibodies can sometimes be overcome. For the ANSER assay, a high titer anti-infliximab antibody at trough is defined as 10 U/ml, for

RIDAscreen the cut-off is 200 ng/ml, for InformTx/Lisa Tracker the cut-off is 200 ng/ml. For other assays, there is insufficient data to define an adequate cut-off for a high titer anti-infliximab antibody.

Differences in assay methodology result in varying sensitivity to detect ADA and discrepancies when reporting ADA titers.[123] Therefore, clinically relevant ADA cut-offs are assay specific, referring mostly to ELISAs and the HMSA (**Table 3**). Vande Casteele et al, showed that ATI >9.1 U/ml (measured with the HMSA) at time of loss of response resulted in a likelihood ratio of 3.6 for an unsuccessful intervention, suggesting these ATI are sustained and probably very hard to overcome.[63] Moreover, Yanai et al. showed ATI >9 µg/mL-eq can identify patients who do not respond to an increased drug dosage with 90% specificity.[10]Additionally, a small retrospective study of IBD patients in whom infliximab was optimized, either proactively or reactively, to overcome immunogenicity showed that an ATI titer < 8.8 U/mL (measured with the HMSA) was associated with drug retention, suggesting that lower titer ATI can often be overcome with dose intensification.[86] A post-hoc analysis of the TAXIT trial showed that ATI> 222 ng/mL eq (measured with an in-house developed drug tolerant ELISA) was not possible to be overcome following infliximab optimization.[120]

Adalimumab

Consensus was reached on all 2 statements regarding adalimumab concentrations and antibodies to adalimumab (**Table 5C**).

22. The minimum drug concentration at week 4 for adalimumab should at least be 5 µg/ml. Drug concentrations greater than 7 µg/ml are associated with an increased likelihood of mucosal healing.

23. During maintenance the minimum trough concentration for adalimumab for patients in remission should be greater than 5 µg/ml. For patients with active disease adalimumab should generally not be abandoned unless drug concentrations are greater than 10 µg/ml.

These drug concentration thresholds were based mainly on adalimumab exposure-response relationship studies depicted in **Table 1**.

Certolizumab pegol

Consensus was reached on all 2 statements regarding certolizumab pegol concentrations and antibodies to certolizumab pegol (**Table 5D**).

24. The minimum concentrations for certolizumab pegol at week 6 should be greater than 32 µg/ml.

25. During maintenance the minimum trough concentration for certolizumab pegol for patients in remission should be 15 µg/ml.

These drug concentration thresholds were based on certolizumab pegol exposure-response relationship studies depicted in **Table 2A**.

Golimumab

Consensus was reached on all 2 statements regarding golimumab concentrations and antibodies to golimumab (**Table 5E**).

26. The minimum drug concentration at week 6 for golimumab should at least be 2.5 µg/ml.

27. During maintenance the minimum trough concentration for golimumab for patients in remission should be greater than 1 µg/ml.

These drug concentration thresholds were based on exposure-response relationship studies depicted in **Table 2B**.

353

354 **Vedolizumab and ustekinumab**

355 Consensus was reached on the statement regarding vedolizumab and ustekinumab
356 concentrations and antibodies to vedolizumab or ustekinumab (**Table 5F**).

357 ***28. Although there are emerging data that may show an association between drug***
358 ***concentrations and outcomes, they are not sufficient to guide specific induction and***
359 ***maintenance drug concentrations for vedolizumab and ustekinumab other than confirming***
360 ***that there is detectable drug.***

361 At the time of the consensus meeting there were only limited data available from exposure-
362 response relationship studies to suggest a clinically relevant vedolizumab (**Table 2C**) or
363 ustekinumab (**Table 2D**) threshold or range associated with favorable therapeutic outcomes.

364

365 **DISCUSSION**

366 Unlike for rheumatoid arthritis and psoriasis, there are only a limited number of biologic
367 agents approved for the treatment of IBD. Additionally, current data demonstrate that patients
368 who fail anti-TNF therapies do no respond as well to subsequent agents.[125, 126] Thus,
369 optimizing the use of biologic therapies is of the utmost importance. TDM is one strategy to
370 optimize biologics and maximise their effectiveness. Reactive TDM can better explain and
371 manage SLR, and there is emerging evidence that proactive TDM further improves outcomes
372 and is being used more frequently.[127, 128]

373 In the recent American Gastroenterological Association guidelines, no
374 recommendation was made regarding proactive TDM of anti-TNFs for patients who have
375 quiescent disease due to a 'knowledge gap'.[96] However, the IBD Sydney Organisation and
376 the Australian Inflammatory Bowel Diseases Consensus Working Group recommended that
377 in patients in clinical remission following anti-TNF therapy induction, TDM should be

considered to guide management and additionally TDM should be considered periodically in patients in clinical remission if the results are likely to impact management.[97] Although well designed large prospective studies are lacking there are preliminary data mainly from retrospective studies which demonstrate that proactive TDM is associated with better therapeutic outcomes compared to empiric dose optimization and/or reactive TDM.[38, 39, 103, 104, 129] Furthermore, numerous retrospective studies[23, 24, 26, 29, 31-33, 67, 73, 74, 77-79, 130, 131] and some post-hoc analyses of RCT[47-49, 71, 76, 94, 132, 133] have shown that higher biologic drug concentrations are associated with favourable short- and long-term therapeutic outcomes in IBD (**supplementary Table 1**, **Table 2** and **Table 3**). There do appear to be certain clinical scenarios that proactive TDM of anti-TNF therapy can efficiently guide therapeutic decisions, such as treatment de-escalation,[134] the application of 'optimized monotherapy' instead of combo therapy with IMM,[82] re-starting therapy after a long 'drug holiday'[135] and treatment cessation upon deep remission.[50, 51]

Nevertheless, before TDM can be widely applied in clinical practice there are several obstacles to their regular use including when to utilize TDM, how to accurately interpret and apply the results of such testing, and in defining the optimal drug concentration thresholds and ranges to target.[136] We feel these consensus statements help address these issues and hope they will aid physicians in better understanding and utilizing TDM.

Major limitations of the evidence and consequently these consensus statements relate to the lack of large prospective studies and RCT on TDM of biologic therapy applied on different IBD phenotypes, and sparse data on induction therapy and on biologic agents other than infliximab and adalimumab. Moreover, it is unclear if trough concentrations are the best predictor of initial response to biologics, compared to peak drug concentrations or total drug exposure. However, in the absence of RCT, consensus guidelines synthesizing the literature and extrapolating from available data serve to support clinicians in clinical decision making.

Further RCT to establish the utility of proactive TDM, particularly during the induction phase, should be performed. Additional future directions should include the development of accurate, easily accessible and affordable rapid assays and dashboards to allow fast dosing adaptation and incorporation of predictive PK models based on patient and disease characteristics.[137, 138]

In conclusion, there is a growing body of evidence that demonstrates the clinical utility of TDM of biologic therapy in IBD. This is a big step towards personalised medicine and optimizing the care of patients with IBD. Although more prospective data are needed especially for proactive TDM, induction therapy, and non-anti-TNF biologics, these consensus statements provide a practical guide to apply TDM for optimizing biologic therapy in patients with IBD.

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841 **Table 1.** Serum adalimumab concentration thresholds associated with therapeutic outcomes

842 in inflammatory bowel disease.

IBD type	Threshold (µg/ml)	Therapeutic outcome	TDM assay	Assay type	Ref.
Induction (week 2)					
CD	>6.7	Clinical remission (w14)	ELISA	AHLC	23
Post-induction (week 4)					
CD	>5	Drug retention	HMSA	Prometheus	29
CD	>12	Normal CRP (≤5mg/L)	ELISA	LFA/ELISA (R-Biopharm AG)	31
UC	≥7.5	Mucosal healing (w10-14)	ELISA	Leuven assay	30
UC	>4.6	Clinical response (w12)	ELISA	Leuven assay	26
UC	>7	Clinical response (w52)	ELISA	Leuven assay	26
Maintenance					
CD	>5.9	Normal CRP (≤5mg/L)	ELISA	AHLC	15
CD	>5.9	Normal CRP (≤3mg/L)	ELISA	Sumitomo Bakelite Co Ltd	16
CD	>8.1	Mucosal healing	HMSA	Prometheus	18
CD	>5.6	Normal CRP (≤3mg/L)	ELISA	In-house	19
CD	>7.9	Mucosal healing	ELISA	In-house	19
CD	>10.3	Mucosal healing	ELISA	In-house	20
CD	>5 (w26)	Clinical remission (w52)	ELISA	Sanquin Diagnostics	21
CD	≥12	Endoscopic remission	HMSA	Prometheus	22
CD	≥12.2	Histologic remission	HMSA	Prometheus	22
CD	≥3.7 (w14)	CRP normalization (w14)	ELISA	AHLC	23
CD/UC	>6.6	Normal CRP (≤5mg/L)	ELISA	AHLC	13

CD/UC	≥6.9	No SLR	RIA	Biomonitor A/S	14
CD/UC	>7.1	Mucosal healing	ELISA	AHLC	13
CD/UC	>4.9	Mucosal healing	ELISA	Theradiag	9
CD/UC	>7.8	Histologic remission	HMSA	Prometheus	12
CD/UC	>7.5	Mucosal healing	HMSA	Prometheus	12
CD/UC	>12.2	Successful dose reduction	ELISA	Promonitor Grifols	11
CD/UC	>9	Clinical response	ELISA	Promonitor Grifols	11
CD/UC	>6.6	Normal CRP (≤5mg/L)	ELISA	Promonitor Grifols	11
CD/UC	>4.5	When SLR, better long-term outcome when change to a biological with a different mechanism of action compare to anti-TNF dosage increase or a switch within class	ELISA	AHLC	10
CD/UC	≥3	No active inflammation[a]	ELISA	AHLC	10
CD/UC	>4.9	When SLR, high risk of failure who subsequently after changing to infliximab	ELISA	Theradiag	8
CD/UC	>7.3	Clinical remission	ELISA	New Zealand assay	7

[a]defined as increased CRP level and/or endoscopic/imaging documentation of inflammation.

ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; CRP: C-reactive protein, TDM: therapeutic drug monitoring; RIA: Radioimmunoassay; SLR: secondary loss of response; TNF: tumor necrosis factor; CD: Crohn's disease; UC: ulcerative colitis; LFA: lateral flow-based assay; Ref.: references, AHLC: antihuman lambda chain.

848 **Table 2.** Association of serum certolizumab pegol, golimumab, vedolizumab and
849 ustekimumab concentration thresholds with therapeutic outcomes in inflammatory bowel
850 disease.

IBD type	Time point	Threshold (µg/ml)	Therapeutic outcome	TDM assay	Assay type	Ref.
A. Certolizumab pegol						
CD	Post-induction (w6)	>31.8	Clinical response/remission (w6)	ELISA	UCB Pharma	94
CD	Post-induction (w6)	>31.9	Normal CRP (≤5mg/L) (w6)	ELISA	UCB Pharma	94
CD	Post-induction (w6)	>32.7	Normal FC (<250mg/g) (w6)	ELISA	UCB Pharma	94
CD	Post-induction (w6)	>34.5	Normal FC (<250mg/g) and CDAI (≤150) (w6)	ELISA	UCB Pharma	94
CD	Post-induction (w6)	>36.1	Normal FC (<250mg/g) and CDAI (≤150) (w26)	ELISA	UCB Pharma	94
CD	Post-induction (w8)	>23.3	Endoscopic remission (w10)	ELISA	UCB Pharma	95
CD	Maintenance (w12)	>13.8	Normal FC (<250mg/g) (w26)	ELISA	UCB Pharma	94
CD	Maintenance (w12)	>14.8	Normal FC (<250mg/g) and CDAI (≤150) (w26)	ELISA	UCB Pharma	94
B. Golimumab						
UC	Induction (w2)	>8.9	Clinical response (w6)	ECLIA	Janssen Biotech Inc	48
UC	Post-induction	>7.4	Clinical response (w6)	ECLIA	Janssen Biotech Inc	48

	(w4)					
UC	Post-induction (w6)	>2.5	Clinical response (w6)	ECLIA	Janssen Biotech Inc	48
UC	Post-induction (w6)	>2.6	Partial clinical response (w14)	ELISA	In house Leuven	93
UC	Maintenance (w28)	>0.9	Clinical remission (w30 and 54)	ECLIA	Janssen Biotech Inc	48
UC	Maintenance (w44)	>1.4	Clinical remission (w30 and 54)	ECLIA	Janssen Biotech Inc	48
C. Vedolizumab						
CD	Induction (w2)	>35.2	Biological remission (w6)	ELISA	Leuven assay	90
UC	Induction (w2)	>28.9	Clinical response (w14)	ELISA	Leuven assay	90
UC	Induction (w2)	>23.7	Mucosal healing (w14)	ELISA	Leuven assay	90
CD/UC	Induction (w2)	≥24.5	No drug optimization (within w24)	ELISA	Theradiag	92
UC	Induction (w6)	>20.8	Clinical response (w14)	ELISA	Leuven assay	90
CD/UC	Induction (w6)	≥18.5	No need for extended therapy	ELISA	Theradiag	92
CD/UC	Induction (w6)	>27.5	Sustained clinical response	ELISA	Theradiag	92
CD/UC	Induction (w6)	>18	Mucosal healing (within w54)	ELISA	Theradiag	91
UC	Post-induction (w14)	>12.6	Clinical response (w14)	ELISA	Leuven assay	90
UC	Post-induction	>17	Mucosal healing	ELISA	Leuven assay	90

	(w14)		(w14)			
CD	Maintenance (w22)	>13.6	Mucosal healing (w22)	ELISA	Leuven assay	90
CD	Maintenance (w22)	>12	Biological remission (w22)	ELISA	Leuven assay	90
D. Ustekinumab						
CD	Post-induction (w8)	>3.3	Clinical remission (w8)	ECLIA	Janssen Biotech Inc	49
CD	Maintenance	>4.5	Endoscopic response	HMSA	Prometheus	89
CD	Maintenance (w24)[a]	>0.8	Clinical remission (w24)	ECLIA	Janssen Biotech Inc	49
CD	Maintenance (w40)[b]	>1.4	Clinical remission (w44)	ECLIA	Janssen Biotech Inc	49

[a]Combined q8w and q12w; [b]q8w only.

ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; CRP: C-reactive protein, FC: fecal calprotectin; ECLIA: electrochemiluminescence immunoassay; w: week; TDM: therapeutic drug monitoring; CD: Crohn's disease; UC: ulcerative colitis; CDAI: Crohn's disease activity index; Ref.: reference.

Table 3. Association of anti-drug antibodies with therapeutic outcomes in inflammatory bowel disease.

Drug	IBD type	ADA	Therapeutic outcome	TDM assay	Assay type	Ref.
IFX	CD	≥282 ng/mL-eq	Lower success rate of treatment optimization	ELISA	Leuven drug-tolerant assay	75
IFX	CD	>8 μg/mL-eq	Shorter clinical response	ELISA	Prometheus	28
IFX	CD	Detectable	Lack of mucosal healing	ELISA	MP Biomedicals	17
IFX	CD	Detectable	Elevated CRP (>5 mg/L)	HMSA	Prometheus	56
IFX	CD	Detectable	Elevated CPP (>5 mg/L)	HMSA	Prometheus	60
IFX	CD	Detectable	Lack of fistula healing	HMSA	Prometheus	12
IFX	CD	Detectable	SLR	ELISA	Prometheus	88
IFX	CD	Detectable	SLR	RIA	Biomonitor A/S	87
IFX	UC	Detectable	Lack of endoscopic response	HMSA	Prometheus	33
IFX	UC	Detectable	Lack of mucosal healing	ELISA	Leuven drug-tolerant assay	67
IFX	CD/UC	≥8.8 U/ml	Drug discontinuation	HMSA	Prometheus	86
IFX	CD/UC	Detectable	PNR	ELISA	AHLC	73
IFX	CD/UC	Detectable	Drug discontinuation	HMSA	Prometheus	63
IFX	CD/UC	>9.1 U/ml	Failure of dose intensification after SLR	HMSA	Prometheus	63
IFX	CD/UC	>12 U/mL	Surgery	HMSA	Prometheus	85
IFX	CD/UC	Undetectable	Mucosal healing	ELISA	AHLC	13
IFX	CD/UC	Undetectable	Short-term clinical response	HMSA	Prometheus	27

IFX	CD/UC	Detectable	SLR	ELISA	AHLC	32
IFX	CD/UC	Detectable	SLR	ELISA	AHLC	84
IFX	CD/UC	>9 μg/mL-eq	When SLR, longer duration of response when anti-TNF agents are switched than when dosage is increased	ELISA	AHLC	10
IFX	CD/UC	≥3.3 U/mL	Lack of post-adjustment endoscopic remission	HMSA	Prometheus	37
IFX	CD/UC	Detectable	Treatment related adverse events	ELISA	Promonitor Menarini / ImmunDiagnostik	83
IFX	CD/UC	Detectable[a]	PNR (w14)	ELISA	AHLC	73
IFX	CD/UC	>4.3 μg/mL-eq[b]	PNR (w14)	ELISA	AHLC	73
IFX	CD/UC	>9.1 U/mL	IFX discontinuation	HMSA	Prometheus	82
IFX	CD/UC	>9.1 U/mL	Infusion reactions	HMSA	Prometheus	82
IFX	CD/UC	>200 ng/mL-eq	No response to treatment optimization	ELISA	Theradiag	81
ADM	CD	Detectable	PNR	ELISA	AHLC	23
ADM	CD	Detectable	Drug discontinuation	HMSA	Prometheus	29
ADM	CD	Detectable	Drug discontinuation	ELISA	In-house	57
ADM	CD	>12 U⁄mL	Lack of clinical response	RIA	Biomonitor A/S	58
ADM	CD	Detectable	Active disease	ELISA	AHLC	15
ADM	CD	Detectable	Higher CRP and ESR	ELISA	Sumitomo Bakelite Co., Ltd	16

ADM	CD	Detectable[d]	No clinical remission (w52)	RIA	Sanquin	21
ADM	CD	Detectable (w12)	Higher needs for dose escalation less frequently sustained clinical benefit due to PNR or SLR	ELISA	R-Biopharm AG	31
ADM	CD/UC	Detectable	Drug discontinuation	RIA	Biomonitor A/S	80
ADM	CD/UC	>4 µg/mL-eq	When SLR, longer duration of response when anti-TNF agents are switched than when dosage is increased	ELISA	AHLC	10
ADM	CD/UC	Detectable	SLR	RIA	Biomonitor A/S	14

[a]either week 2 or 6; [b]week 2; [c]Université François-Rabelais, Immuno-Pharmaco-Genetics of Therapeutic Antibodies, Tours, France; [d]week 26.

ADA: anti-drug antibody; IFX: infliximab; ADM: adalimumab; ELISA: enzyme-linked immunosorbent assay; CD: Crohn's disease; UC: ulcerative colitis; CRP: C-reactive protein; RIA: Radio-immunoassay; eq: equivalent; SLR: secondary loss of response; U: units; HMSA: homogeneous mobility shift assay; ESR: erythrocyte sedimentation rate; AHLC: antihuman lambda chain antibody; TDM: therapeutic drug monitoring; TNF: tumor necrosis factor; w: week; PNR: primary non-response; Ref.: references.

880 **Table 4.** Scenarios of applying therapeutic drug monitoring of biological therapy in patients
881 with inflammatory bowel disease.

Statement	**Vote agreement, %**
A. Anti-TNFs	
1. It is appropriate to order drug/antibody concentration testing, in responders at the end of induction for all anti-TNFs.	92 (12/13)
2. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on all anti-TNFs.	100 (13/13)
3. It is appropriate to order drug/antibody concentration testing of anti-TNFs at the end of induction in primary non-responders.	100 (13/13)
4. It is appropriate to order drug/antibody concentration testing for all anti-TNFs, in patients with confirmed secondary loss of response.	100 (13/13)
B. Vedolizumab	
5. It is appropriate to order drug/antibody concentration testing for vedolizumab, in responders at the end of induction.	15 (2/13)[a]
6. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on vedolizumab.	46 (6/13)[a]
7. It is appropriate to order drug/antibody concentration testing for vedolizumab in non-responders at the end of induction.	92 (12/13)
8. It is appropriate to order drug/antibody concentration testing for vedolizumab, in patients with confirmed secondary loss of response.	83 (10/12)[a]
C. Ustekinumab	
9. It is appropriate to order drug/antibody concentration testing for ustekinumab, in responders at the end of induction.	39 (5/13)[a]

10. It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on ustekinumab.	31 (4/13)[a]
11. It is appropriate to order drug/antibody concentration testing for ustekinumab in non-responders at the end of induction (at 8 weeks).	92 (12/13)
12. It is appropriate to order drug/antibody concentration testing for ustekinumab, in patients with confirmed secondary loss of response.	83 (10/12)[a]

[a]After a second round of voting.

TNF: tumor necrosis factor

900 **Table 5.** Biological drug concentrations and anti-drug antibodies when applying therapeutic
901 drug monitoring in inflammatory bowel disease.

Statement	**Vote agreement, %**
A. General	
13. There is no difference in indication for ordering drug/antibody concentrations or interpretation of results for biosimilars or the originator drug.	100 (13/13)
14. The threshold drug concentration may vary depending on disease phenotype and desired therapeutic outcome.	100 (13/13)
15. In the presence of adequate trough drug concentrations, anti-drug antibodies are unlikely to be clinically relevant.	100 (12/12)
16. Other than for anti-infliximab antibodies, there are not enough data to recommend a threshold for high anti-drug antibody titers for the biologic drugs.	100 (12/12)
B. Infliximab	
17. The current evidence suggests that the variability of infliximab concentrations between the different assays is unlikely to be clinically significant.	100 (13/13)[a]
18. There is insufficient evidence that inter-assay drug concentration results are comparable for biologic drugs other than for infliximab.	100 (13/13)
19. The minimal trough concentration for infliximab post-induction at week 14 should be greater than 3 μg/ml, and concentrations greater than 7 μg/ml are associated with an increased likelihood of mucosal healing.	100 (13/13)
20. During maintenance the minimal trough concentration for infliximab for patients in remission should be greater than 3 μg/ml. For patients with active disease infliximab should generally not be abandoned unless drug concentrations are greater than 10 μg/ml.	92 (12/13)

21. In the absence of detectable infliximab, high titer anti-infliximab antibodies require a change of therapy. Low level antibodies can sometimes be overcome. For the ANSER assay, a high titer anti-infliximab antibody at trough is defined as 10 U/ml, for RIDAscreen the cut-off is 200 ng/ml, for InformTx/Lisa Tracker the cut-off is 200 ng/ml. For other assays, there is insufficient data to define an adequate cut-off for a high titer anti-infliximab antibody.	100 (13/13)
C. Adalimumab	
22. The minimum drug concentration at week 4 for adalimumab should at least be 5 μg/ml. Drug concentrations greater than 7 μg/ml are associated with an increased likelihood of mucosal healing.	83 (10/12)[a]
23. During maintenance the minimum trough concentration for adalimumab for patients in remission should be greater than 5 μg/ml. For patients with active disease adalimumab should generally not be abandoned unless drug concentrations are greater than 10 μg/ml.	100 (12/12)
D. Certolizumab pegol	
24. The minimum concentrations for certolizumab pegol at week 6 should be greater than 32 μg/ml.	100 (12/12)
25. During maintenance the minimum trough concentration for certolizumab pegol for patients in remission should be 15 μg/ml.	92 (11/12)
E. Golimumab	
26. The minimum drug concentration at week 6 for golimumab should at least be 2.5 μg/ml.	92 (11/12)
27. During maintenance the minimum trough concentration for golimumab for patients in remission should be greater than 1 μg/ml.	92 (11/12)
F. Vedolizumab / Ustekinumab	

28. Although there are emerging data that may show an association between drug concentrations and outcomes, they are not sufficient to guide specific induction and maintenance drug concentrations for vedolizumab and ustekinumab other than confirming that there is detectable drug.	100 (12/12)

902 [a]After a second round of voting.

903 HMSA: homogeneous mobility shift assay; TNF: tumor necrosis factor.

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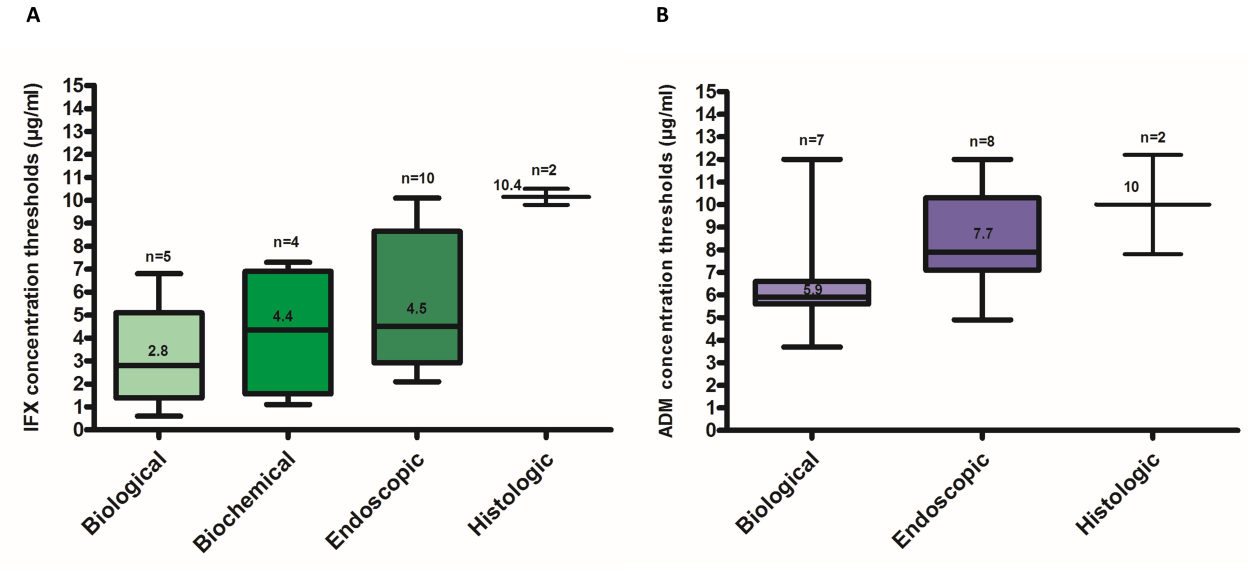
Figures

Figure legend 1. Infliximab (A)[13, 17, 20, 40-43, 45, 46, 53, 55, 59-61, 64, 67] and adalimumab (B)[9, 11-13, 15, 16, 18-23, 30, 31] concentration thresholds associated with biological (based on CRP), biochemical (based on FC), endoscopic or histologic remission in inflammatory bowel disease. Box whisker plots show the median (solid line within box), interquartile range (upper and lower box boundaries) and 5-95% lower and upper extreme (whiskers).

Figure footnote 1. IFX: infliximab; ADM: adalimumab; CRP: C - reactive protein; FC: fecal calprotectin.



Supplementary Table 1. Serum infliximab concentration thresholds associated with therapeutic outcomes in inflammatory bowel disease.

IBD type	Time point	Threshold (μg/mL)	Therapeutic outcome	TDM assay	Assay type	Ref.
Induction						
CD	w2	>16.9[a]	Clinical response (w14)	ELISA	Theradiag	77
CD	w2	>9.2	Clinical remission (w14)	ELISA	AHLC	24
CD	w2	>23.1	Endoscopic remission (w12)	ELISA	Leuven assay	76
CD	w2	>20.4[a]	Clinical remission (w14)	ELISA	Theradiag	77
CD	w2	>9.2	Fistula response (w14)	ELISA	AHLC	74
CD	w2	>9.2	Fistula response (w30)	ELISA	AHLC	74
UC	w2	>21.3	Clinical remission (w14)	ELISA	Mitsubishi Tanabe Pharma Corp	78
UC	w2	≥28.3	Mucosal healing (w10-14)	ELISA	Leuven drug-tolerant assay	67
UC	w2	<16.5	Colectomy	ELISA	Leuven assay	79
UC	w2	>11.5[a]	Clinical response (w14)	ELISA	Theradiag	77
UC	w2	>11.5[a]	Clinical response (w30)	ELISA	Theradiag	77
UC	w2	>15.3[a]	Clinical remission (w14)	ELISA	Theradiag	77
UC	w2	>14.5[a]	Clinical remission (w30)	ELISA	Theradiag	77
UC	w2	≥18.6	MES<2 (w8)	ELISA	Janssen Biotech Inc	130
CD/UC	w2	<6.8	PNR (w14)	ELISA	AHLC	73
CD	w6	>10	Endoscopic remission (w12)	ELISA	Leuven assay	76
CD	w6	>7.2	Fistula response (w14)	ELISA	AHLC	74
CD	w6	>8.6	Fistula response (w30)	ELISA	AHLC	74
CD	w6	>2.2	Drug retention beyond one year of treatment	ELISA	AHLC	24
UC	w6	≥15	Mucosal healing (w10-14)	ELISA	Leuven drug-tolerant assay	67
UC	w6	>6.6	Endoscopic response (w8)	ELISA	Sanquin Diagnostics	33
UC	w6	>22	Clinical response (w8)	ELISA	Janssen Biotech Inc	47
CD/UC	w6	<3.5	PNR (w14)	ELISA	AHLC	73
CD/UC	w6	<13	ATI formation	HMSA	Prometheus	63
Post-induction						
UC	w8	>41.1	Clinical response (w8)	ELISA	Janssen Biotech Inc	47

CD	w10	≥9.1	Drug retention (w52)	HMSA	Prometheus	72
CD	w14	>12.7	Fistula response (w24)	ELISA	Dynacare Laboratories	36
CD	w14	>3.5	Clinical response (w54)	ELISA	Janssen Biotech Inc	71
CD	w14	<1	SLR (w54)	ELISA	Janssen Biotech Inc	70
CD	w14/22	>3	Sustained clinical response	ELISA	Matriks Biotek	69
UC	w14	>2.5	Colectomy-free survival	ELISA	In house Leuven	68
UC	w14	≥2.1	Mucosal healing (w10-14)	ELISA	Leuven drug-tolerant assay	67
UC	w14	≥2.1	Mucosal healing (w10-14)	LFA	R-Biopharm AG	66
UC	w14	>5.1	Clinical response (w30)	ELISA	Janssen Biotech Inc	47
UC	w14	>3.2[a]	Mucosal healing	ELISA	Theradiag/Matriks Biotek	65
UC	w14	>3.2[a]	Steroid-free remission	ELISA	Theradiag/Matriks Biotek	65
CD/UC	w14	>5.5	Clinical remission (w54)	HMSA	Prometheus	64
CD/UC	w14	<2.2	Treatment failure	HMSA	Prometheus	63
CD/UC	w14	<6.2	Loss of response (w48)	HMSA	Prometheus	62
Maintenance						
CD	w30	≥3	Mucosal healing (w26)	ELISA	Janssen Biotech Inc	61
CD		>2.8	Normal CRP (≤5mg/L)	HMSA	Prometheus	60
CD		≥2.2	Normal CRP (≤5mg/L)	HMSA / ELISA	Prometheus	59
CD		≥9.7	Endoscopic remission	HMSA / ELISA	Prometheus	59
CD		≥9.8	Histologic remission	HMSA / ELISA	Prometheus	59
CD		>0.6	Normal CRP (≤0.3mg/dL)	ELISA	MP Biomedicals	17
CD		>1.1	Normal FC (<300µg/g)	ELISA	MP Biomedicals	17
CD		>4	Mucosal healing	ELISA	MP Biomedicals	17
CD		<3	Mean CDAI increase ≥70	HMSA	Prometheus	56
CD		>2.7	Mucosal healing	ELISA	In-house	20
CD		>1.5	Clinical remission	ELISA	Theradiag	55
CD		>3.4	Normal CRP (≤5mg/L)	ELISA	Theradiag	55
CD		>5.7	Normal FC (<59µg/g)	ELISA	Theradiag	55
CD		<1.8	Significant endoscopic recurrence	ELISA	AHLC / Theradiag	54
CD		>10.1	Fistula healing	HMSA	Prometheus	53
CD		>10.1	Mucosal healing	HMSA	Prometheus	53
CD		≥2.5	Relapse after anti-TNF withdrawal	ELISA	Matriks Biotek	52

CD		≥6	Relapse after anti-TNF withdrawal	ELISA	Leuven assay	51
CD		≥2	Relapse after anti-TNF withdrawal	ELISA	In-house	50
UC	w30	>2.4	Clinical response (w54)	ELISA	Janssen Biotech Inc	47
UC		>3	Normal FC (<250mg/g)	ELISA	LFA Bühlmann / Sanquin	46
UC		>3	Mucosal healing	ELISA	LFA Bühlmann / Sanquin	46
UC		≥7.5	Endoscopic healing	HMSA / ELISA	Prometheus	45
UC		≥10.5	Histologic healing	HMSA / ELISA	Prometheus	45
CD/UC		<0.5	SLR	RIA	Biomonitor A/S	44
CD/UC		>6.8	Normal CRP (≤5mg/L)	ELISA	AHLC	13
CD/UC		>5	Mucosal healing	ELISA	AHLC	13
CD/UC		>7.3	Normal FC (<250mg/g)	ELISA	Immunodiagnostik	43
CD/UC		>8.3	Mucosal healing	HMSA	Prometheus	42
CD/UC		>4.1	Clinical remission	ELISA	In-house	41
CD/UC		>2.1	Clinical remission	ELISA	Theradiag	40
CD/UC		>2.9	Clinical remission and normal CRP (≤5mg/L)	ELISA	Theradiag	40
CD/UC		>3.9	Clinical remission and normal FC (<250mg/g)	ELISA	Theradiag	40
CD/UC		>4.9	Clinical remission, normal CRP (≤5mg/L) and normal FC (<50 mg/g)	ELISA	Theradiag	40
CD/UC		≥5	Drug retention	ELISA/ HMSA	Prometheus	39
CD/UC		<3.5	Treatment failure	HMSA	Prometheus	38
CD/UC		<4.6	IBD-related hospitalization	HMSA	Prometheus	38
CD/UC		<1.8	Detectable ATI	HMSA	Prometheus	38
CD/UC		<6.3	Serious infusion reaction	HMSA	Prometheus	38
CD/UC		>3.8	When SLR, better long-term outcome when change to a biological with a different mechanism of action compare to anti-TNF dosage increase or a switch within class	ELISA	AHLC	10
CD/UC		≥4.5	Post-adjustment endoscopic remission	HMSA	Prometheus	37
CD/UC		>5	Lower risk for an IBD-related surgery and dose escalation or drug cessation for SLR after withdrawal of the immunomodulator	ELISA	Leuven assay	35
CD/UC		<3	ATI formation	ELISA	Sanquin Diagnostics	34
CD/UC		>5.1	Clinical remission	ELISA	New Zealand assay	7

CD/UC		>5.4	Endoscopic remission	ELISA	Leuven	25

[a]Infliximab biosimilar CT-P13; [b]Université François-Rabelais, Immuno-Pharmaco-Genetics of Therapeutic Antibodies, Tours, France.

ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; CRP: C-reactive protein, FC: fecal calprotectin; TDM: therapeutic drug monitoring; RIA: Radioimmunoassay; AHLC: antihuman lambda chain antibody; SLR: secondary loss of response; CDAI: Crohn's disease activity index; CD: Crohn's disease; UC: ulcerative colitis; IBD: inflammatory bowel disease; LFA: lateral flow-based assay; ATI: antibodies to infliximab; w: week; TNF: tumor necrosis factor; PNR: primary non-response; Ref.: reference; MES: Mayo endoscopic score.